In re Application of: Jerachmiel Appelbaum
Serial No.: 10/550,681
Filed: September 26, 2005
Office Action Mailing Date: January 29, 2008

Examiner: Benjamin J. Packard
Group Art Unit: 4173
Attorney Docket: 30667

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-33 are in this case. Claims 1-18 and 26-33 have been withdrawn from further consideration as being drawn to non-elected invention and species. Claims 19-25 have been examined on the merits, with TPEN and tumor invasive metastases as the elected species. The Examiner is kindly requested to consider Applicant's remarks hereinbelow with respect to claims reading on the elected invention and species.

Claims 19-23 and 25 have been rejected under 35 U.S.C. § 102. Claim 24 has been rejected under 35 U.S.C. § 112. Claims 19, 25 and 33 have been canceled herewith. Claims 20, 22, 23 and 24, as well as claims 26-32 have been amended herewith.

Election/Restriction

The Examiner has stated that claims 1-18 and 26-33 are withdrawn from further consideration as being drawn to a non-elected invention and species and that claims 19-25 are now examined.

Applicant wishes to note that in response to the Restriction Office Action mailed November 2, 2007, Applicant has elected Group II, **claims 19-33**, as the invention to be examined. Applicant selected TPEN and tumor invasion metastasis as elected species. Applicant has indicated that claims 19-28 read on the elected invention and species.

The Examiner has noted in the instant Office Action that claims 26-33 are withdrawn from further consideration.

Claims 29-33 read on methods of treating conditions other than tumor invasion metastasis and hence read on non-elected **species**.

Claims 26-28 read on a method that utilizes a TPEN-Germanium complex, or organic or inorganic Germaniun alone, and hence read on non-elected **species**.

Applicant respectfully requests that the Examiner's statement with regard to claims being examined on the merits will be reconsidered accordingly.

Applicant further wishes to emphasize that claims 26-33 should be considered as reading on non-elected **species** and that upon allowance of the examined claims, these claims should also be examined. Applicant asserts that these claims belong to the elected invention, as defined in the above-mentioned Restriction Office Action. The Examiner is referred in this regard to the section entitled *"additional amendments"* hereinbelow, in which amendments introduced to these claims are discussed.

35 U.S.C. § 112 second Paragraph Rejection

The Examiner has stated that claim 24 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 24 has been amended.

Specifically, the Examiner has stated that Claim 24 recites the limitation "the cyclooxygenase" in line 2 and that there is insufficient antecedent basis for this limitation in the claim or claim 22, from which it depends, or claims 19-21, from which claim 22 depends from, respectively.

Claim 24 has been amended so as to correct a typographical error and to depend from claim 23 (instead of from claim 22). Claim 23 recites "pathological condition influenced by the action of Cyclooxygenases" and therefore includes the antecedent basis for the limitation of claim 24.

It is noted herein that claim 23 has been amended so as to depend from claim 20. Nonetheless, amended claim 23 recites cyclooxygenases as antecedent basis for claim 24.

Applicant therefore believes to have overcome the Examiner's rejection.

35 U.S.C. § 102(b) Rejection – Ferdinandy et al.

The Examiner has stated that claims 19-23 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Ferdinandy et al. The Examiner's rejection is respectfully traversed. Claims 19, 21 and 25 have been canceled. Claims 20 and 22-24 have been amended.

Specifically, the Examiner has stated that Ferdinandy et al. discloses the use of TPEN (a pharmaceutical agent) to make nitros-oxide free radicals which then inactivate iron-sulphur-centered enzymes (a metalloprotease) (page 500, right column, about lines 14-18 of the cited document). The Examiner has further stated that one pathological condition influenced by the matrix metalloproteases is ischemic/reperfused hearts, which were treated with TPEN (page 498 "Effects of TPEN on cardiac function in ischemic/reperfused hearts" of the cited document).

Ferdinandy et al. teach the beneficial effect of TPEN on post-ischaemic cardiac function and dysrhythmias. Ferdinandy et al. note that the TPEN benefical effects are due to a TPEN-mediated inhibition of NO accumulation in ischemic/reperfused myocardium. Ferdinandy et al. further note that the NO-dependent toxicity may result, in part, due to "*...**the formation of NO-derived free radicals species** such as peroxynitrite anion, **the inactivation of iron-sulphur-centered enzymes** involved in mitochondrial respiration processes, early reactive hyperaemia mediated by a substantial increase in NO release, and during the accumulation of neutrophils expressing the inducible NO synthase*" (see, page 500, right column, line 14-19, of the document). Ferdinandy et al. further note that "*[a]lthough the exact mechanism of action of TPEN is unknown, it has been suggested that the metal chelator, **TPEN, is able to reduce the ischemia and reperfusion-induced injury by eliminating or preventing the formation of toxic free radicals** during cardiac surgery in the reperfused myocardium*" (see, page 500, right column, lines 20-24 of the document). Thus, Ferdinandy et al. imply that TPEN eliminates or prevents the formation of nitros-oxide free radicals and thereby prevents nitros-oxide free radicals-related toxicity. It is therefore concluded from the teachings of Ferdinandy et al. that administration of TPEN leads to the **activation** of iron-sulphur-centered enzymes, by reducing the levels of nitros-oxide free radicals in the myocardium.

In sharp distinction, the instant application teaches the utilization of TPEN for chelating metals which are essential cofactors of MMPs, and for abolishing NO production which leads to **inactivation** of MMPs (see, page 10, lines 18-21 of the instant application). As taught throughout the instant application, the therapeutic

activity of TPEN in the treatment of diseases where MMPs has a pathological role is attributed to the TPEN-mediated MMPs **inactivation**.

Ferdinandy et al. fail to teach a role of TPEN for the inhibition of MMPs, but rather, by suggesting that TPEN enhances MMPs activity, actually teaches away from the present invention.

Ferdinandy et al. therefore fail to teach the use of TPEN in treating conditions in which **inhibition** of MMPs is beneficial.

Ferdinandy et al. further fail to teach the use of TPEN derivatives or TPEN complexes with anti-free radical metals in treating conditions in which **inhibition** of MMPs is beneficial.

Notwithstanding the above, and in order to expedite prosecution and to more clearly distinct the claimed invention from the teachings of Ferdinandy et al., Applicant has chosen to amend the claims so as to read on the use of TPEN for the treatment of a list of pathological condition that are affected by inhibition of MMPs. The indicated conditions do not recite ischemic reperfusion injury.

Thus, claim 20 has been amended so as to indicate treatable conditions. Claim 21 has been canceled for reciting limitations now added to amended claim 20. Claim 22 has been amended so as to depend from amended claim 20.

In addition, Applicant has chosen to cancel claims 19 and 25, without prejudice.

Applicant believes that the claimed invention is not anticipated by Ferdinandy et al. and is therefore allowable.

35 U.S.C. § 102(e) Rejection – Fernandez-Pol et al.

The Examiner has stated that claims 19-23 and 25 are rejected under 35 U.S.C 102(e) as being anticipated by Fernandez-Pol et al. (U.S. Patent No. 6,803,379). The Examiner's rejection is respectfully traversed. Claims 19, 21 and 25 have been canceled. Claims 20 and 22-24 have been amended.

Specifically, the Examiner has stated that Fernandez-Pol et al. disclose that TPEN causes apoptosis in cellular replication and refers to Paragraph [0022] of the document which recites "... *[a] number of investigators have shown that apoptosis*

can be induced if the intracellular level of Zn^{2+} are reduced using chelators. For example N,N,N',N'-tetrakis-2-pyridyl methyl-ethylene diamine (TPEN) added to the culture cells induces apoptosis...".

The Examiner has further stated that this is applicable for treating many diseases, including cancer and metastasis, and refers to Paragraph [0081] and Example 1 at Paragraph [0401] of the document. The Examiner has further stated that at Paragraph [0472] of the document the increase of COX-2 levels in solid tumors is noted.

Fernandez-Pol et al. teach the use of metal chelating agents for disruption and inactivation of specific transition metal ion containing zinc finger structural motifs and catalytic sites in metalloproteins, for the treatment of diseases produced by intoxication with heavy metals. The metal chelating agents taught by Fernandez-Pol et al. are furoic acid, 2-thiophenecarboxylic acid and derivatives, analogs and structurally related chemicals thereof.

Although Fernandez-Pol et al. mentions in passing TPEN as being a metal chelator which can induce apoptosis, the concept taught in this patent has been exemplified only for furoic acid, 2-thiophenecarboxylic acid and derivatives, analogs and structurally related chemicals thereof.

Furthermore, on Paragraph [0018], cited by the Examiner, it is specifically stated that the chelators mentioned therein are not specific to zinc and that the information related to these chelators (e.g., TPEN) provide no clear indication of the role of zinc in apoptosis.

Moreover, in Paragraph [0018] of the document, it is specifically recited that "*... apoptosis can be **induced** if the intracellular level of Zn2+ are **reduced** using chelators*".

Thus, Fernandez-Pol et al. (i) fail to show the effect of TPEN in the treatment of pathological conditions associated with inhibition of MMPs; and (ii) teaches away a role for TPEN as reducing apoptosis by inhibiting MMPs activity.

It is noted in this regard that it is well known in the art that MMPs are **apoptosis inducing** and that inhibiting MMPs results in **reduced apoptosis**.

In sharp distinction, the instant invention teaches TPEN and derivatives thereof as inhibitors of MMPs, which can be used in the treatment of pathological conditions where inhibition of MMPs is therapeutically beneficial. As widely discussed in the instant application (see, for example, page 17, lines 1-7 of the instant invention) TPEN is a perffered metal chelator for the treatment of the indicated pathological conditions, due to (1) the TPEN ability to bind zinc, iron, and copper and not magnesium and calcium, thus not interfering with normal physiological functions which involve magnesium and calcium; and (2) the high lipid solubility of TPEN which enables high permeability thereof through cellular membranes.

Indeed, as further widely demonstrated in the instant application, TPEN was found to be highly effective in reducing angiogenesis, cancer cell invasiveness and metastases (see, Examples 1-4).

The present invention therefore relates to TPEN and derivatives thereof as agents that inhibit MMPs activity and thus **reduce** apoptosis.

Applicant has chosen, in order to expedite prosecution, to cancel claims 19 and 25. Claim 20 has been amended and claim 21 has been canceled, as delineated hereinabove. Claim 22 has been amended so as to depend from amended claim 20.

Claims 23 and 24 have also been amended, as delineated above.

Since Fernandez-Pol et al. fail to teach TPEN or derivatives thereof as metal chelator for the treatment of pathological conditions where inhibition of MPPs, and thus reduction of apoptosis, is therapeutically beneficial, it is clear that the claimed invention is not anticipated by Fenandez-Pol et al. and is therefore allowable.

Additional amendments

Applicant has chosen to further amend claim 20 by reciting the TPEN derivatives described in the instant application (see, for example, page 10, third paragraph, claim 18 and claim 28).

Applicant has further chosen to amend claim 23 so as to depend from claim 20.

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Applicant has noticed that claims 27 and 28 (currently marked as withdrawn, for reading on non-elected species) erroneously depend from claim 25 instead of from claim 26 and has chosen to correct these typographical errors.

Applicant has further chosen to amend claim 26 (currently marked as withdrawn, for reading on non-elected species) so as to read on a complex formed from TPEN or a TPEN derivative and a metal selected from the group consisting of selenium, gallium, molybdenum, manganese, iron, cobalt and germanium. Support for this amendment is found, for example, on the second and third paragraphs on page 10 of the instant application.

Accordingly, claim 28 has further been amended so as to recite TPEN derivatives.

Applicant has further chosen, in order to expedite prosecution, to amend claims 29-32 (currently marked as withdrawn, for reading on non-elected species) so as to read on methods utilizing TPEN or a derivative thereof as a highly specific zinc chelator. Consequently, claim 33 has been canceled.

Applicant has further chosen to amend claim 32 so as to depend from claim 31. Applicant contends that this amendment is merely cosmetic.

Examination of generic claims

In view of the amendments made to the claims and the arguments recited herein it is believed that the claims are allowable with respect to the elected species and hence examination of claims 20-33 in their generic context and with respect to all the species recited therein is respectfully requested.

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In view of the above amendments and remarks, it is respectfully submitted that amended claims 20, 22-24 and 26-32 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

Martin D. Moynihan
Registration No. 40,338

Date: July 29, 2008

Encl:

- Petiton for Extension for Three (3) Months Time